

The 35 U.S.C. § 112, second paragraph, rejections

The Examiner rejected claims 5 and 27 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 27 has been amended as suggested by the Examiner at page 1 of the Office Action. The Examiner's suggested amendments to claim 5, to substitute a comma with a semicolon between parts a) and b) and after the term "media" in part b), are reflected in pending claim 5 (see the Preliminary Amendment filed on April 26, 1999 and the Amendment and Response filed on July 12, 2001). Therefore, withdrawal of the 35 U.S.C. § 112, second paragraph, rejections is respectfully requested.

The 35 U.S.C. §§ 101/112 rejection

The Examiner rejected claims 5-6, 24 and 26-31 under 35 U.S.C. § 101, alleging that the claimed invention is not supported by a specific or substantial asserted utility or a well established utility. In addition, the Examiner rejected claims 5-6, 24 and 26-31, and objected to the specification, under 35 U.S.C. § 112, first paragraph, asserting that the specification fails to adequately teach how to use the instant invention. These rejections are respectfully traversed.

The claims are directed to human 4-1BB protein having SEQ ID NO:2 and soluble forms thereof, e.g., the extracellular domain of SEQ ID NO:2.

Specifically, the Examiner alleges that, in the absence of supporting evidence, one skilled in the art would not accept that the structural relatedness of human 4-1BB (H4-1BB) to murine 4-1BB would indicate that H4-1BB and murine 4-1BB would have similar activities or uses, as 1) individual members of polypeptide families can have distinct, opposite biological activities, and 2) function cannot be predicted based solely on structural similarity to a protein in a sequence database.

"Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record." See page 1098 in section II(B)(2)(a)(2) of the Revised Utility Examination Guidelines (Fed. Reg., 66, 1092 (2001)). Moreover, "[a]n applicant need only provide one credible assertion of specific and substantial utility ... to satisfy the utility requirement." Id.

Murine 4-1BB is disclosed as a 256 amino acid protein which is expressed in murine

splenocytes, T cell clones and hybridomas (page 7, lines 26-27 of the specification). 4-1BB expression was inducible in cloned T cells by antigen receptor stimulation and in resting T cells by activators which deliver a complete growth stimulus (page 7, lines 29-31 and page 8, lines 16-20). 4-1BB was not expressed on resting T cells (page 8, line 16). Further, it is disclosed that the activation of 4-1BB by anti-4-1BB antibodies indicates that 4-1BB functions as an accessory molecule in T cell activation and proliferation (page 9, lines 19-24).

Structurally, murine 4-1BB protein has a 23 amino acid leader sequence, a 26 amino acid membrane anchor segment, and 19 cysteine residues (see Figure 1). Based on its structure, it is disclosed that 4-1BB protein is related to members of the nerve growth factor receptor (NGFR) superfamily, such as CD40 and CD27 (page 8, lines 29-37).

To obtain DNA encoding a human homolog of murine 4-1BB, Applicant prepared degenerate primers based on a comparison of the amino acid sequences of a number of members of the NGFR superfamily, i.e., mouse 4-1BB, human NGFR, human tumor necrosis factor receptors, human CD40 and human CD27 (page 14, lines 28-35). The primers were employed in an amplification reaction using cDNA prepared from RNA isolated human peripheral blood lymphocytes as the template (page 15, lines 21-29). A specific 240 bp PCR product was obtained, which was the expected size of H4-1BB DNA if that region of H4-1BB is similar to mouse 4-1BB (page 15, lines 31-33). The PCR fragment was cloned, sequenced, and used as a probe to screen a cDNA library of activated human T lymphocytes (page 15, lines 30-39). The nucleotide sequence of the isolated cDNA, and putative amino acid sequence encoded thereby, is disclosed in Figure 2 (H4-1BB). H4-1BB is a 255 amino acid protein. The relative positions of cysteine residues in the extracellular portion of H4-1BB are almost identical to those in murine 4-1BB, and the position of a hydrophobic region in the carboxy-terminal half of H4-1BB (residues 187-213) corresponds to the membrane anchor segment in murine 4-1BB.

Figure 3 in the specification shows various pairs of molecules which are present on the cell surface of antigen presenting cells (APC) or T cells, and which bind to a specific molecule on the other type of cell, e.g., 4-1BB on T cells bind to 4-1BBL on APC and CTLA4 or CD28 on T cells bind to B7 on APC. Figure 5 illustrates how soluble forms of one of the pair, e.g., a soluble form of 4-1BB (4-1BBAP) or CTLA (CTLA Ig), can prevent binding of the natural ligand, 4-1BB and CTLA, respectively, to its receptor, 4-1BB-L and B7, respectively. Applicant

discloses that H4-1BB like murine 4-1BB will be co-stimulating for T cell activation (page 16, line 38-page 17, line 1).

The specification also discloses that the blocking of the interaction of CD28 on T cells with B7 on B cells suppresses antibody production and cell-mediated immune responses (page 17, lines 27-30), and that Linsley et al. (Science, 257, 792 (1992), a copy is enclosed herewith) report that the use of a soluble form of a T cell activation molecule (CTLA-4 which binds B7) can result in immunosuppression (page 5, lines 8-16). Linsley et al. prepared a soluble form of the human T cell costimulatory molecule CTLA-4 (CTLA4Ig) and relate that it binds to B7. The administration of CTLA4Ig to mice suppressed T cell-dependent antibody responses to two antigens. Linsley et al. conclude that the soluble form of CTLA is a potent immunosuppressive agent that can be employed clinically as an immunosuppressive drug, e.g., to manipulate immunity to transplants and in the treatment of antibody-mediated autoimmune diseases (page 794). Applicant discloses that a soluble form H4-1BB is useful to block binding of H4-1BB to its ligand, which results in immunosuppression (page 17, line 36-page 18, line 3).

In addition, the specification discloses that tumors may not deliver adequate co-stimulatory signals for full activation of T cells (page 5, lines 22-25). The specification relates that Townsend et al. (Science, 259, 368 (1993), a copy is enclosed herewith) disclose that expression of B7 on melanoma cells induced tumor rejection. Applicant discloses that an antibody against H4-1BB may have the same effect (page 5, lines 30-32).

Thus, one of skill in the art in possession of Applicant's specification would recognize that a similar approach to that described in Linsley et al. and Townsend et al. could be used for other pairs of receptor/ligands present on T cells and APC, e.g., murine 4-1BB and its receptor and the human homolog of murine 4-1BB, H4-1BB, and its receptor. Therefore, Applicant has provided two credible assertions of a specific and substantial utility for H4-1BB.

To support the assertion that individual members of polypeptide families can have distinct, opposite biological activities, the Examiner cites Vukicevic et al. (Proc. Natl. Acad. Sci. USA, 93, 9021 (1996)), Massagué (Cell, 49, 437 (1987)), Pilbeam et al. (Bone, 14, 717 (1993)), and Kopchick and Chen (U.S. Patent No. 5,350,836). While individual members of polypeptide families may have distinct, biological activities, none of the documents cited by the Examiner stand for the proposition that species homologs have unrelated activities.

Moreover, evidence that murine 4-1BB and H4-1BB have common properties is provided in WO 99/36093 and Zhou et al. (Immunol. Lett., 45, 67 (1995)) (a copy of each is enclosed herewith). WO 99/36093 and Zhou et al. disclose that H4-1BB expression on T cells is inducible and is observed on activated T cells and a soluble form of H4-1BB binds to a ligand on other immune cells, respectively. And, as discussed below, results with murine 4-1BB are viewed by the art as predictive of results with H4-1BB.

To support the assertion that function cannot be predicted based solely on structural similarity to a protein in a sequence database, the Examiner cites to Skolnick and Fetrow (Trends in Biotechnol., 18, 34 (2000)), Bork (Genome Research, 10, 398 (2000)), Doerks et al., Trends in Genetics, 14, 248 (1998)), Smith and Zhang (Nature Biotechnology, 15, 1222 (1997)), Brenner (Trends in Genetics, 15, 132 (1999)), and Bork and Bairoch (Trends in Genetics, 12, 426 (1996)). Regardless, none of these documents evidence that the function of a recognized homolog is wholly unpredictable.

Evidence that the art worker would accept sequence similarity as a means to predict species homologs is provided by Schwarz et al. (Gene, 134, 295 (1993), a copy is enclosed herewith). Schwartz et al. report the sequence of a human cDNA ("ILA") which was obtained from a library of activated HTLV-1 transformed human T lymphocytes. The ILA protein has one amino acid difference relative to Applicant's SEQ ID NO:2. Based on the sequence of ILA, Schwartz et al. relate that ILA is "a new member of the human nerve-growth-factor receptor/tumor-necrosis-factor receptor family" (abstract) and the "likely human homologue of the murine 4-1BB" (page 296).

Evidence that the art worker would be of the opinion that properties of murine 4-1BB are reasonably predictive of uses for H4-1BB is provided in Strome et al. (Journal of Immunotherapy, 23, 430 (2000)), Sica and Chen (pages 355-362, "Cancer Gene Therapy: Past Achievements and Future Challenges", Nagy A. Habib, ed., in Advances in Experimental Medicine and Biology, Vol. 465, Kluwer Academic/Plenum Publishers, New York (2000)), and Melero et al. (Nat. Med., 3, 682 (1997)) (a copy of each is enclosed herewith).

Melero et al. relate that monoclonal antibodies against murine 4-1BB eradicated established tumors in mice. Melero et al. point out that prior to their report, several monoclonal antibodies that stimulate the immune system, anti-CD3, anti-CD28 and anti-CTLA-4, had

antitumor effects *in vivo* (page 682; citing to Ellenhorn et al., Science, 242, 569 (1988); Townsend et al., Science, 259, 368 (1993); and Leach et al., Science, 271, 1734 (1996)) (a copy of each is enclosed herewith). Based on their results, Melero et al. conclude that "a similar approach, based on the use of monoclonal antibodies to human 4-1BB, holds promise for clinical applications in cancer treatment" (page 684).

Strome et al. describe the synergistic effect of CD28 and 4-1BB costimulation (via anti-CD28 and/or anti-4-1BB antibodies) in augmenting T-cell activation and enhancing the efficacy of tumor-specific effector T cells in a mouse melanoma model where the melanoma is poorly immunogenic (page 431). They conclude that co-stimulation of tumor-draining lymph node T cells through CD28 and 4-1BB increases their potential for cancer immunotherapy (abstract).

Sica and Chen relate that 4-1BB (referred to as CD137) is a potent T cell costimulatory molecule that can synergize with the B7-CD28 pathway (page 357). They further discuss that nonstimulating blocking 4-1BB antibodies can be used to downregulate chronic rejection reactions and lessen the doses of anti-rejection agents to promote graft survival in transplant patients (page 360).

Thus, although murine 4-1BB and H4-1BB have about 65% amino acid sequence identity, the art clearly recognizes that murine 4-1BB and H4-1BB are homologs and there is evidence that murine 4-1BB and H4-1BB have properties in common. Further, based on the immunosuppressive and anti-tumor properties of anti-murine 4-1BB antibodies, the art worker accepts that ligands that activate H4-1BB or block the binding of H4-1BB to its receptor, e.g., antibodies to H4-1BB, will likewise be useful.

Therefore, Applicant's assertion that H4-1BB-based methods would be useful to suppress an immune response or to enhance an anti-tumor response would be viewed by the art worker as credible.

In view of the remarks herein, withdrawal of the rejection of the claims under 35 U.S.C. §§ 101 and 112, first paragraph, is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone

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Applicant's attorney (612-373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 15 day of November, 2001.

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